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Regulatory and Trade  
Counsellors

November 30, 1998

By Fax

Dr. Larry G. Hart  
Executive Secretary  
NTP Board of Scientific Counselors  
P.O. Box 12233  
Research Triangle Park, NC 27709

Dear Dr. Hart:

**Comments to the RoC Subcommittee of the  
NTP Board of Scientific Counselors on the proposal to list  
"Alcoholic Beverages" in the 9th Report on Carcinogens**

Multinational Business Services is an international regulatory consulting firm that specializes in the procedures utilized by federal agencies to develop regulations and supporting information. Anheuser-Busch has asked our firm to review the process utilized by the National Toxicology Program ("NTP") to review alcohol beverages for possible listing in the *9th Report on Carcinogens*. The comments presented here are the result of our review.

Anheuser-Busch, Inc. is the world's largest brewer. As a company and industry leader, Anheuser-Busch is committed to promoting responsible use of its products. Every year, Anheuser-Busch sponsors a number of programs designed to remind its customers that responsible drinking by adults is the only acceptable drinking practice. For example, Anheuser-Busch sponsors "Family Talk About Drinking", a program consisting of a guidebook and video developed by authorities in the areas of education, alcohol treatment, and family counseling; "Caring Connections", a step-by-step guide to help concerned lay people, educators and others make a positive difference in the lives of at-risk children; and "Training for Intervention Process", a program that trains bartenders, waiters, waitresses, and convenience store clerks in responsible serving techniques in an effort to help prevent alcohol abuse, drunk driving and underage drinking. Any information regarding the safety of its product is always a concern to Anheuser-Busch.

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We recognize the importance of the NTP listing and welcome the opportunity to participate in the NTP comment process. We would like to take advantage of this opportunity to urge NTP to make determinations for listing in a manner consistent with its statutory mandate by performing a thorough review and independent analysis of the relevant literature.

NTP's responsibility for comprehensive review in carcinogenesis determinations is set forth in the Preamble to the *8th Report on Carcinogens*, which states: "Considerations regarding carcinogenicity in humans or experimental animals are based on scientific judgment with consideration given to all relevant information." The Introduction to that Report notes that the reports "serve as meaningful compilations of data on the carcinogenicity of the listed substances in humans and/or animals . . . ."

We recognize that it is the official position of NTP that listing a substance in the Report does not establish that the substance presents a risk to persons in their daily lives. As NTP has stated in the Preamble to the *8th Report on Carcinogens*: "Risk assessments are not conducted by the National Toxicology Program for substances in the Report. The listing of a substance in the Report, therefore, does not establish that any such substance presents a risk to persons in their daily lives."

It is, however, widely acknowledged that the public may rely on the Report on Carcinogens ("RoC") as "one of the few major sources of objective, peer-reviewed information on carcinogenic substances."<sup>1</sup> As such, the RoC might be relied upon by the public as standing for the proposition that a substance presents a risk to them when used in their daily lives even though this is not the message NTP intends to convey. This public reliance makes it likely that a determination of carcinogenicity by NTP would have an impact on Anheuser-Busch and could have an overall net negative impact on public health, contrary to the fundamental purpose of the Report.

The potential for consumer confusion is particularly acute in the context of alcohol beverages. Alcohol beverages have been consumed for centuries and are part of a daily diet for many adult consumers, the vast majority of whom consume responsibly. A stark pronouncement by NTP that alcohol beverages are carcinogenic could confuse consumers who are unaware that NTP's determination is merely a hazard identification and does not establish that alcohol beverages present a risk to persons in their daily lives. This would be particularly true if NTP were to say nothing about the level of consumption on which any listing was based. NTP also needs to reconcile its message with the scientific literature establishing that alcohol beverage consumption can be associated with health benefits for consumers.<sup>2</sup>

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<sup>1</sup> Synthetic Organic Chem. Mfrs Ass'n v. Dep't of Health and Human Services, 720 F.Supp. 1244, 1248 (W.D. La. 1989). See also *8th Report on Carcinogens*, Introduction at 1 ("The People of the United States of America, concerned with the relationships between their environment and cancer have asked, through the U.S. Congress, for information about substances that cause cancer or might cause cancer.").

<sup>2</sup> See Pearson TA, "Alcohol and Heart Disease", Am. Heart Ass'n Science Advisory, *Circulation* 94(11):3023-25 (1996); Klatsky AL, "Epidemiology of Coronary Heart Disease - Influence of Alcohol", *Alc. Clin. Exp. Res.* 18(1):88-96 (1994).

Although the RoC is a hazard identification document, it is clear from the legislative history of the Congressional directives establishing the Program that Congress intended that the Department should provide some indication of the relative potency and risk of an agent under review where possible.<sup>3</sup> We believe that the Department has the discretion to indicate such information in the listing itself in appropriate cases. As stated in the Draft Background Document, "[p]otential health benefits of low alcohol beverage consumption should be recognized as well as the detrimental effects of heavy consumption."<sup>4</sup> Since NTP recognizes the validity and importance of the information surrounding the health benefits of alcohol beverage consumption, this information should be reflected in the RoC listing.

The reliance of the public and other agencies on the RoC emphasizes the importance of the NTP process and makes it even more clear that any NTP determination to list a substance as a carcinogen must be made after a thorough peer review. NTP should produce an objective, peer-reviewed Report that is based on a systematic and accurate evaluation of all of the available information.

The NTP listing process is judicially reviewable under the Administrative Procedure Act. NTP is obligated to comply with its listing criteria. These criteria are considered law during a judicial review process and an agency must comply with them in the determination process.

After reviewing the Draft RoC Background Document, we have several questions and concerns about the evaluation process performed by NTP in determining whether to list alcohol beverages as a carcinogen. The following questions are raised by a review of the Draft ROC Background Document.

1. What criteria does NTP use in making a determination of the sufficiency of the evidence for classifying an agent as a "known human carcinogen"?
2. Is the NTP analysis based on an objective and independent review and analysis of all available literature, or is it an arbitrarily selective method of review?
3. Does the NTP review the studies it relies upon in a consistent manner?
4. Is the NTP determination consistent with the findings of other agencies?

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<sup>3</sup> "The committee intends that this should be a comprehensive document containing an updated list of all known or suspected carcinogenic agents, the nature of exposure and the approximate number of persons exposed to such agents. The relative toxicity of such agents should be described, to the extent such information is known, whether or not any of these act synergistically, the levels of exposure to be expected from certain occupations, geographic areas, food or consumer goods, and the identification of subpopulations expected to be at higher than average risk." H.R. Rep. No. 1192, 95th Cong. 2d Sess. at 28 (1978). "It is the committee's intent that any such list include not only the name of the substance, but the data which supports the inclusion of each compound on the list, any uncertainties in the data yet to be resolved, and where possible, estimates the [sic] magnitude of the risk each poses." *Cong. Rec.* Oct. 10, 1978, p. 34938.

<sup>4</sup> "Draft RoC Background Document for Alcoholic Beverage Consumption", p. 3-4 (Dec. 2-3, 1998).

Each of these questions raises issues about the reliability and consistency of the NTP review process. Each issue will be addressed briefly in these comments.

1. **What criteria does NTP use in making a determination of the sufficiency of the evidence for classifying an agent as a "known human carcinogen"?**

The criteria for listing a substance as a "known human carcinogen" require that there be "sufficient evidence from studies in humans which indicates a causal relationship. . . ." However, at no time during this process has NTP disclosed to the public or manufacturers what criteria it uses to determine causation. The most accepted criteria for determining causation are the Bradford Hill criteria. These include strength of association, consistency, specificity, biologic gradient (dose-response), and biologic plausibility and coherence.

As stated by Dr. Emanuel Rubin, a noted authority on alcohol and health, in his comments to the NTP submitted in response to the February 3, 1998 *Federal Register* notice:

In the case of alcohol abuse and cancer, important Hill Criteria have not been met. The strengths of the associations remain weak, and the results of many studies are inconsistent. A dose-effect relationship is elusive, and if present seems to operate only at levels consistent with alcohol abuse. The biological plausibility is questionable, in view of the lack of molecular similarity of ethanol to known carcinogens, its failure to produce experimental cancers, and its lack of mutagenicity.<sup>5</sup>

Another problem in responding to a proposed listing stems from the difficulty in proving a negative. As stated by Dr. Rubin in his comments: "The postulated link between alcohol consumption and cancer of any organ is based upon epidemiological studies that claim an association. Philosophically, if one wishes to take issue with such conclusions, it is indeed difficult to prove a negative, i.e. no weak association. Nevertheless, the burden of proof should be on those who claim an effect of alcohol."<sup>6</sup>

It is also notable that the Federal Courts have addressed the standards necessary for reliability and admissibility of scientific evidence. The widely accepted standard for reliability of evidence as set forth by the Supreme Court in *Daubert v. Merrell Dow Pharmaceuticals* is "whether the reasoning and methodology underlying the testimony is scientifically valid."<sup>7</sup> In considering the scientific validity of epidemiological evidence the Federal Judicial Center recommends that courts look at the strength of the association between the exposure and disease, temporal relationships,

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<sup>5</sup> Hereinafter "Rubin Comments."

<sup>6</sup> Rubin Comments at 2.

<sup>7</sup> 509 U.S. 579, 113 S. Ct. 2786, 125 L.Ed.2d 469 (1993).

consistency of an association with other research, biological plausibility of association (such as mechanism of action), the ability to rule out other explanations, and dose-response relationship.<sup>8</sup>

2. **Is the NTP analysis based on an objective and independent review and analysis of all available literature, or is it an arbitrarily selective method of review?**

NTP's gathering of information seems to consist of picking out a few available studies and concluding that since there are studies that show an association between consumption of alcohol beverages and cancer it must be a human carcinogen. NTP does not even consider a majority of the available scientific studies, and dismisses many studies based on a selection method that seems arbitrary, subjective and without scientific support.

For example, NTP sets forth its search strategy for literature on alcohol beverage consumption and cancer in Appendix 1 to the Draft RoC Background Document. NTP claims to have identified 958 studies, and then reduced the number to 777 by eliminating studies from before 1987 (the date of publication of the International Agency for Research on Cancer Monograph on Alcohol Drinking). Our review identified over three thousand publications that examine the potential relationship between alcohol beverage consumption and cancer published after 1987. NTP does not provide the full bibliography of citations it identified, so it is not possible to determine if its search was comprehensive. In addition, even though NTP states that it eliminated studies from before 1987 from its search, it cites 35 such papers in its analysis and only 23 post-1987 papers.

It is possible that NTP's method of review has been forced by the limited time frame that was allowed for the review process. The ten months from the notice of proposed listing on February 3, 1998 to the hearing date on December 2 and 3, 1998 -- and the far more limited time for RoC Subcommittee review -- do not provide enough time for a thorough review and analysis of even a portion of the vast available literature. This limited time frame forces NTP to reach a conclusion without performing a complete and independent review of the literature. Because of the importance of this issue, we urge NTP to extend this time frame so that it is able to review all of the scientific information available about the postulated relationship between consumption of alcohol beverages and cancer.

There does not seem to be any clear scientific rationale for NTP's selection of studies for inclusion in its analysis of the postulated carcinogenicity of alcohol beverage consumption. Certainly, NTP does not provide sufficient information to make a determination as to what system it used for selecting the information it chooses to rely upon. It is therefore impossible to view the NTP review process as a comprehensive, objective and independent peer-review of the available information relating to consumption of alcohol beverages and cancer.

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<sup>8</sup> Federal Judicial Center, *Reference Manual on Scientific Evidence* (1994). The RoC is often used as a foundation document in litigation, however, NTP's proposal that exposure to alcohol beverages is causally related to cancer in humans clearly does not satisfy many of these criteria and therefore should not be deemed an adequate basis to support scientific expert testimony in any court case.

There is also a problem inherent in all studies dealing with alcohol beverages and cancer in that there are many possible confounders that must be considered in dealing with a dietary substance. These confounders are often related to other dietary habits. As stated by Dr. Emanuel Rubin in his comments to the NTP submitted in response to the February 3, 1998 *Federal Register* notice: "Considering the fact that many studies have linked cancers of the upper respiratory tract to low levels of fruits, vegetables, vitamins, minerals and micronutrients in the diet, the failure to control for dietary confounders in alcohol abusers remains a problem."<sup>9</sup> The Draft Background Document does not take into account this potential for dietary confounders.

Further questions are raised by the heavy reliance of the NTP review on the Longnecker and Tseng study "Alcohol and Cancer" ("the Longnecker study").<sup>10</sup> The Longnecker study is not an appropriate source for the NTP review because it has not been subjected to traditional peer review at this time. Because the Longnecker study uses unorthodox methods to select, aggregate, adjust, and interpret the data and present findings, it is particularly important that it be peer-reviewed and analyzed.

3. Does the NTP review the studies it relies upon in a consistent manner?

A review of the Draft RoC Background Document reveals several inconsistencies in the method of review of studies performed by NTP in making its proposed determination of carcinogenicity. First, NTP does not examine the cohort studies for some of the cancers, but does examine them in the context of breast cancer. In addition, NTP relies on Longnecker's statement that it is not possible to reach a conclusion as to the postulated association between alcohol and breast cancer because no mechanism can be identified.<sup>11</sup> NTP fails, however, to make this same distinction in dealing with cancers at other sites.

In addition, for some of the types of cancer reviewed in the Report, a minimum number of cases is required to make a study valid for consideration by NTP. Again, this requirement is not applied consistently and is not applied for other types of cancers.

Another problem with the NTP review is that there is an inconsistency inherent in an analysis which dismisses the literature on alcohol beverages and lung cancer on the grounds that it cannot be trusted because of confounding issues, and yet relies on head and neck cancer studies that have the same problem.

Finally, another inconsistency that is immediately apparent is that the determination is said to be for alcohol beverages while the sections on Experimental Carcinogenesis, Genotoxicity, and Other Relevant Data provide studies on ethanol.

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<sup>9</sup> Rubin Comments at 2-3.

<sup>10</sup> The Longnecker study is attached to the Draft RoC Background Document as Appendix III.

<sup>11</sup> Draft Background Document, Attachment III at 28.

4. Is the NTP determination consistent with the findings of other agencies?

NTP has often said that it is merely performing a hazard identification process and that the RoC list is meant only to provide information to the public and to other agencies to use in conducting risk assessments. In fact, the Preamble to the *8th Report on Carcinogens* states:

The listing of a substance in the Report is descriptive and qualitative in nature and represents an initial step in hazard identification, which is generally considered the first step in the analytical process known as risk assessment. It is necessary to conduct a risk assessment in order to estimate the potential for any substance to harm human health. Risk assessments are not conducted by the National Toxicology Program for substances in the Report. The listing of a substance in the Report, therefore, does not establish that any such substance presents a risk to persons in their daily lives. Such risk assessments are properly the purview of the appropriate Federal, State, and local health regulatory and research agencies.<sup>12</sup>

This raises a question as to the purpose of the review of the consumption of alcohol beverages by NTP. Alcohol is one of the most highly reviewed and regulated substances in history. Alcohol beverages are widely studied and regulated by numerous agencies, including the National Institute on Alcohol Abuse and Alcoholism, the National Cancer Institute, the Department of Health and Human Services, the Bureau of Alcohol, Tobacco and Firearms, and the United States Department of Agriculture. In fact, the National Institute on Alcohol Abuse and Alcoholism is a federal agency dedicated to alcohol-related issues. The Government spends millions of dollars annually for research on alcohol, alcohol abuse and related topics.

NTP itself stated in its introduction to the *Seventh Annual Report on Carcinogens* that alcohol beverages are "not included in this Report because . . . [s]everal publications issued by the National Cancer Institute explain the relationship of alcoholic beverages . . . to cancer." In the *8th Report on Carcinogens* NTP stated that "[r]eports issued by the National Cancer Institute or the IARC explain the relationship of alcoholic beverages . . . to cancer."

Alcohol beverages have also been examined at the state level. For example, on July 1, 1988, the State of California added to its list of Chemicals Known to the State to Cause Cancer or Reproductive Toxicity (under the Safe Drinking Water and Toxic Enforcement Act of 1986) the following: "*Alcoholic Beverages, when associated with alcohol abuse.*" It is notable that California made the important distinction between alcohol beverages and alcohol abuse in this listing. This acknowledges the key roles of confounding and level of consumption that are reflected in the epidemiologic literature.

This is the first time that NTP has proposed listing a foodstuff in the Report on Carcinogens. This departure from NTP's traditional role of studying occupational or environmental contaminants as potential carcinogens presents new issues and problems that the NTP review process is not designed to address. This new venture into complex dietary substances presents many problems not

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<sup>12</sup> *8th Report on Carcinogens*, Summary at 1 (1998).

only because of the difficulties within the NTP process (which has never before dealt with a foodstuff), but also because of the difficulties inherent in analyzing studies and drawing conclusions relating to dietary substances. For example, many investigators believe that cancer risks are influenced by diet, yet they are unable to specify or quantify these relationships. The potential carcinogenicity of dietary factors such as fat, total calories, obesity and nutrient deficiencies has been the subject of much speculation and study.

One final concern that we have with regard to the NTP process is the lack of involvement by scientists with expertise in alcohol and dietary issues. Based on the record that we have reviewed, it appears that the decisions regarding listing of carcinogens are made by scientists without recognized expertise in dietary and alcohol issues. Alcohol beverages are not like other substances that have been examined by NTP in the past, and the nature of this substance and of the NTP review process dictates a review by scientists with expertise in these areas.

In summary, we believe that NTP's review is inadequate. It is clear that alcohol beverages differ substantially from the substances that NTP has considered for listing in the past. Alcohol beverages are highly regulated substances, and there is a vast body of literature addressing the postulated relationship between consumption of alcohol beverages and cancer. We urge the NTP's committees to carefully review all scientific research on alcohol and health before reaching a conclusion about listing alcohol beverage consumption in its RoC. If necessary, the committees should extend the time period for review to enable NTP to perform a complete and accurate review and analysis of the relevant literature.

Until NTP is able to clarify its determination of the sufficiency of evidence for classifying an agent as a "known human carcinogen", complete an objective and independent review and analysis of all available literature, apply consistency in selecting and reviewing the studies it relies upon, and conform its process to the actions of other agencies, the Subcommittee members must vote against the proposed listing.

We will appreciate your careful consideration of these comments on an important public health matter.

Sincerely,



Jim J. Tozzi  
Director